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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/827,121	BAXTER ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/11/2005, 04/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on 08/09/2006), Applicants filed a response received on 09/14/2006. Claims 61-82 are pending in this instant Office action.

Election

2. Applicant's election with traverse of Group I, (Claims 66, 76, 78, 80 and 82) in the reply filed on 09/14/2006 is acknowledged. Claims 61-65, 67-75, 77, 79 and 81 are linking claims. The traversal is on the ground(s) that each product in the Groups is not "different inventions" and does not have "serious burden". This is not found persuasive because each Group represents a distinct independent invention by the virtue of distinct proteins co-crystals and further containing structural information identified by the Appendix number, which represents a distinct protein 3-D structure. Consequently, a different search is required for the data of each Appendix and the corresponding 3-D structures. Searching altogether would require a serious search burden on the examiner. The requirement is still deemed proper and is therefore made FINAL.

Claims 61-82 are pending in the instant application. Claims 66, 76, 78, 80 and 82 will be examined herein only to the extent they read on the elected subject matter.

In order to clarify the record, it is noted that linking claims 61-65, 67-75, 77, 79, and 81 link inventions of Groups I, II, III, IV, V, and VI. In the previous office action, the

examiner inadvertently indicated that the linking claims link only the inventions of Group I and VI.

Priority

3. Applicant's claim for the benefit of a continuation application of prior application 09/637,132 filed on 08/10/2000 (now abandoned), which claims benefit of application of 08/980,115 filed on 11/26/1997 (now US Patent 6,266,622), which claims benefit of application 08/764,870 filed on 12/13/1996 (now US Patent 6,236,946), which claims benefit of provisional applications 60/008,606 filed on 12/14/1995, 60/008,540 filed on 12/13/1995 and 60/008,543 filed on 12/13/1995 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

4. Information disclosure statements (IDS) filed on 01/11/2005 and 04/25/2006 have been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. References not considered were lined through because paper copies were not located in the prior filed applications. Examiner requests that applicant provide a copy of each reference not considered in response to this office action.

Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The structural coordinates in Appendices 3-8 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID No. must be inserted into the description of the Appendix or into the Appendix directly.

The SEQ. ID NOs are required in Figure 3 for each polypeptide. Appropriate correction is required.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or

1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID No.

Objections to the Specification

6. The specification is objected to because of the following informalities:

a. The specification is objected to because the title is not descriptive of the claims. A new title is required that is clearly indicative of the invention to which the claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example:

---A method of using a model of a ligand bound nuclear hormone receptor or ligand binding domain thereof---

b. In page 9 line 2, page 75 line 14 and page 76 line 23, the instant specification recite "GC-1" whereas the Appendix 8 in page 365 recites "GC-2" for describing a ligand complexed with the human TR-β-LBD. Appropriate clarification is required.

Claim Objections

7. Claim 67 is objected to because of the following informalities: The citation of "Forrier" in the Claim 67 should be ---Fourier---. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 75-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims75-77, 79-80 (claims 78 and 81 dependent therefrom) recite the limitation "high resolution". However, the term "high" is a relative term, which renders the claim indefinite. The term "high resolution" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 61-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 61-62 (claims 64-74 dependent therefrom), claim 75 (claim 76 dependent therefrom), claim 77 (claim 78 dependent therefrom), claim 79 (claim 80 dependent therefrom), claim 81 (claim 82 dependent therefrom) are drawn to methods comprised of

using a model of a nuclear hormone receptor, a model ligand binding domain and/or a nuclear hormone receptor ligand wherein the method steps comprising: providing structural information from a nuclear hormone receptor crystallography with or without a ligand, using a structural information of a model representing a nuclear hormone receptor, or using a structural information from homology models of any nuclear hormone receptor related protein disclosed in top of page 17. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that species are adequately described to represent the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Claims 66, 76, 78, 80 and 82, the disclosed structural coordinates represent species from broad genus model of any nuclear hormone receptors, *i.e.,* the structural coordinates of the rat thyroid hormone receptor defined by a polypeptide SEQ ID NO: 1. However, the claims 66, 76, 78, 80 and 82 also includes step of using structural information from a model or a structurally homologous models compared to disclosed atomic coordinates according to respective independent

claims. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed methods of use structural coordinates of any nuclear hormone receptor, any thyroid receptor, any thyroid receptor isoform, or any thyroid receptor ligand binding domain, which encompasses species that are widely variant in structure. While it is acknowledged that claims 66, 76, 78, 80, and 82, limit the structural data to Appendix 3, it is noted that the claims have been interpreted as encompassing the use of those coordinates for producing homology models, which also encompass widely variant structures. As such, the disclosure of representative species of structural coordinates as disclosed in Appendix 3-8, which describes the three-dimensional structure of rat thyroid hormone receptor or human thyroid hormone receptor is insufficient to be representative of the attributes and features of all species of structure coordinates and models thereof encompassed by the recited genus method of using three-dimensional structure information based on any crystals or any model of structural coordinate of said receptors including any homology model. In this case, the specification does not provide any structural information commonly possessed by members of the genus which distinguish the species within the genus of structural coordinates or models thereof from others such that one can visualize or recognize the identity of the members of the genus. Given the lack of description of a representative number of actual structural coordinate, models of structural coordinate and/or models from a homologous structure coordinate, the

specification fails to sufficiently describe the claimed method in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

10. Claims 61-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using a model of thyroid hormone receptor having the structural coordinates of Appendix 3-8, does not reasonably provide enablement for the broad scope of claimed method comprised of using a model of any nuclear hormone receptor, any model ligand binding domain, including any thyroid receptor or binding site thereof wherein the method steps encompass: providing structural information from a nuclear hormone receptor, which includes crystallization of a nuclear hormone receptor with or without a ligand, using structural information of a model representing a nuclear hormone receptor, or using a structural information from homology models of any nuclear hormone receptor related protein.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on

the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: The claims are so broad as to encompass methods comprised of using a model of any nuclear hormone receptor, a model any ligand binding domain of said receptors and a model of any thyroid receptor or binding domain thereof wherein the method steps comprise: providing structural information which has been interpreted as including crystallography with or without any ligand, using a structural information of model representing any nuclear hormone receptor, or using a structural information from homology models of any nuclear hormone receptor related protein with an expectation that the possible ligand will have the ability to bind to the receptor. The broad scope of claimed methods is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nuclear hormone receptors 3-D structures, including homology model structures thereof. In this case the disclosure is limited to a method of using a model of thyroid receptor having the structural coordinates of Appendix 3-8 for identifying a thyroid hormone receptor.

(B) The nature of the invention: The invention depends on using structural coordinates to identify nuclear hormone receptor ligands or other nuclear hormone receptors by identifying some structural feature of the ligands that is "predicted to result in an altered property." Thus, the nature of the invention relies heavily on the structure of the receptor structural coordinates in identifying ligands and optionally predicting some structural feature that will result in an altered property with an expectation that alteration of that structural feature will achieve that altered property.

(C) The state of the prior art; (D) The level of one of ordinary skill; and (E) The level of predictability in the art: At the time of the invention, methods of using known structural coordinates of nuclear hormone receptors for highly homologous receptors were known in the art as evidenced by Zechel et al. (1994, March 15, The EMBO Journal, vol. 13, p. 1425-1433) and McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336). The techniques of using known structural coordinate to study a ligand for designing an altered property were well within the skill level of one of skill in the art. However, the ability to use homology models in ligand identification or screening with an expectation that the model represents a biologically relevant receptor was highly unpredictable. The problems of modeling includes "the fitting together of protein domains in a multi-domain protein, the determination of the most likely conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking – to name only a few" (see middle of page 25 of Flower, Darren R., Drug Design Cutting Edge Approaches, Published by The Royal Society of Chemistry, 2001). While methods of displaying a three dimensional structure of protein and displaying binding pocket of a protein using a set of structure coordinates was known, Lambert et al. (US Patent Application Publication 2004/0137518) acknowledges that "potential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, §0017). Also, the ability to predict the three-dimensional structure of a polypeptide was highly unpredictable (see, *e.g.,* Branden et al. "Introduction to Protein Structure 2nd Ed.," Garland Publishing Inc., New York, 1999, p. 350). The instant claims have been interpreted as encompassing crystallization of

nuclear hormone receptor proteins. At the time of the invention, methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as

evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Along these same lines, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of a protein having widely variant nuclear hormone receptors and a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of a nuclear hormone receptor can be achieved using any crystallization parameters.

(F) The amount of direction provided by the inventor and (G) The existence of working examples: MPEP states, "[t]he amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." As stated above, the state of the art at the time of the invention was well-developed with respect to methods of using structural coordinate for altering structure of proteins or ligands. However, as noted above, the ability to predict the three-dimensional structure of a protein based on the structure of another protein was highly unpredictable as evidenced by the prior art. Also, the ability

to predict structural regions of any protein with an expectation of obtaining a desired effect was also highly unpredictable as evidenced by the prior art.

In this case, the specification fails to compensate for the high level of unpredictability in the art. The specification fails to teach sufficient working example of the broad claimed invention. While the specification teaches working examples of using models having the structural coordinates of Appendix 3-8, it is noted that these examples are not sufficient to enable models of all nuclear hormone receptors and their isoforms as disclosed in claims. While MPEP § 2164.02 states, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed," MPEP § 2164.02 acknowledges that "[l]ack of a working example...is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." In this case, the unpredictability in the art is very high as evidenced by the prior art and the absence of a working example is considered relevant in making the determination of an enabling disclosure. Further, it is noted that, while the specification provides guidance regarding changes in ligand structure that may result in altering thyroid hormone receptor activity, there is no guidance provided in the specification that any method of using a model based on one of these sets of structural coordinates will achieve an expected altered ligand property using homology modeling to identify at least one structural part wherein an alteration in said structural part is predicted to result in an altered nuclear hormone receptor function.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: It was not routine at the time of the invention to generate

all three-dimensional structures of any nuclear receptor independently or using the three-dimensional structure of thyroid hormone receptors as a template for homology modeling. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use a method of using all model structures as encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

As such, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the modeling structure and use of modeled structure and ligand interaction to have desired biological influence is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting- 35 USC § 101

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

11. Claims 76,78, 80 and 82 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 10, 11 and 22, respectively, of prior U.S. Patent No. 6,266,622. This is a double patenting rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 61-75, 77, 79, and 81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,266,622. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the US patent and the patent is claiming common subject matter, as follows: Instant claims 61-75, 77, 79, and 81 are anticipated by claims 1-28

of US Patent No. 6,266,622 which discloses a method for identifying a compound capable of selectively modulating the activity of a thyroid hormone receptor (TR) isoform comprising: modeling test compounds into TR LBD isoform using a structural model of TRLBD isoform, screening said test compounds in a biological assay, and identifying a test compounds that modulates the activity of a TR isoform and having further disclosed additional limitations from U.S. Patent No. 6,266,622.

13. Claims 61-82 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,236,946. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the US patent and the patent is claiming common subject matter, as follows: Instant claims 61-82 are anticipated by claims 1-22 of US Patent No. 6,236,946 which discloses a method of designing a nuclear receptor synthetic ligand comprising: generating model nuclear receptor ligand binding domain using Figure 28, which is identical to instant Appendix 3 and having further disclosed additional limitations from U.S. Patent No. 6,236,946.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 61-62, 65, 67-68, 70-71, 73 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by reference by Zechel et al. (1994, March 15, The EMBO Journal, vol. 13, p. 1425-1433) as evidenced by Spanjaard et al. (1991, Proc. Natl. Acad. Sci. USA, vol. 88, p. 8587-8591). Claims 61-62, 65, 67-68, 70-71, 73 and 74 are drawn to a method of using a model of nuclear hormone receptor or ligand binding domain (LBD) thereof, bound to a nuclear hormone receptor ligand comprising: providing structural information of corresponding receptor and accessing the structural information (claim 61) with further limitations disclosed in dependent claims. A method of determining whether a potential ligand binds to the said receptor comprising: accessing structural informations of said receptor binding domain and ligand, modeling biding of ligand and the receptor (claim 62) with further limitations disclosed in dependent claims.

The instant specification and claims do not exclude DNA or Zinc as being a ligand, thus an instant ligand encompasses a DNA and/or zinc of Zechel et al. Zechel et al. teach a method of using a model of a nuclear hormone receptor and ligand binding domain "based on the three-dimensional structure of GR (glucocoticoid receptor) and ER DBD-DNA (estrogen receptor DNA binding domain) complexes" derived from a co-crystal complex and "modeling of the dimerization interfaces involved in the cooperative binding of RAR (retinoic acid receptor), RXR (retinoid X receptor) and TR DBDs (thyroid hormone receptor DNA binding domains) predicts that the receptor DBD contributing the CII finger region (RXR) has to be bound to 5' to its partner which contributes either

the T-box region --- or the CI finger region" of the ligand DNA (see bottom left column, p. 1430). According to instant specification, the nuclear receptors disclosed by Zechel al. are part of a nuclear receptor superfamily (see page 2, lines 1-4). Thus the method of Zechel et al. teaches limitations comprising: providing and accessing structural information of an atomic coordinate model of the nuclear hormone receptor and ligand binding domain, modeling the ligands DNA and zinc to a nuclear hormone receptor "ligand binding domain" (claims 61-62, 65, 68, 70-71, 73 and 74). The Zechel et al. reference teaches a method "based on the three-dimensional structure of" "Luise et al., 1991" who teach a step of solving "the glucocorticoid receptor DNA-binding domain complexed with DNA" (see Abstract and p. 1429, Fig. 4 caption) which necessarily involves performing a Fourier transformation of crystallographic data, thus a method of Zechel et al. meet the limitation of claim 67. The method of Zechel et al. meets all limitations of claims 61-62, 65, 67-68, 70-71, 73 and 74 as described above.

15. Claims 61-65, 67-69, and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336). The instant claims are drawn to a method of using a model of a nuclear hormone receptor and ligands using an atomic coordinate of nuclear binding receptor or a nuclear binding receptor domain.

McKinney teaches a method of using "computer graphic models of ligand-TBPA binding pocket complexes" (see description of Figure 3, p. 329) as shown in Figure 3, page 329, by "a high-resolution X-ray crystallographic structure of one of the transport

protein, thyroxine binding prealbumin (TBPA)" (see bottom of right column, p. 327). Claims must be given their broadest reasonable interpretation according to MPEP 2111. In this case, the specification does not disclose a specific definition for a nuclear hormone receptor or a thyroid receptor, but discloses that a nuclear receptor is a receptor for , e.g., thyroid hormones (see specification column bridging pages 16-17). McKinney's disclosure that TBPA is a receptor for thyroxine (a thyroid hormone), see p. 327, right column and disclosure of "TBPA and at least one thyroid hormone nuclear receptor have a considerable number of their properties in common or have aspects of similarity" (see middle left column, p. 330), the TBPA (binding pocket used in the method of McKinney) is considered to be a nuclear hormone receptor binding pocket. Thus, McKinney teaches a method of using a model of a nuclear hormone receptor ligand, binding domain, ligand binding domain or a TR isoform thereof and a ligand bound. McKinney teach that "the binding site matches the structure and chemistry of the hormone with great precision, which together with the fact that TBPA almost completely engulfs the hormone" (see top of left column, p. 328, lines 6-9) and meets the limitations of claims 63-64. The structure model of McKinney is based on high-resolution X-ray crystallographic structure (see p. 329, Figure 3 caption), which necessarily used a Fourier transformation of X-ray crystallographic data, thus meets the limitation of claim 67. In Figure 3 of McKinney shows "the nonphenolic (tyrosyl) ring of THs (thyroid hormones) appears to be suitable (somewhat rigid, sterically accessible aromatic ring that is polarizable) for undergoing a stacking interaction" (see top of right column, p. 328, lines 14-19) thus meets the limitations of claims 68-69. Interaction of

ligands (four different ligands) in the binding pocket thus meets the limitations of claim 68, 69 and 71. The Thyroxine (T3) used in modeling by McKinney has all the chemical features required by the instant Formula 1 disclosed in the instant specification page 3 as shown in Figure 1, page 325 of McKinney, thus meets the limitation of claim 72. Therefore, McKinney teaches all the claim limitations of Claims 61-65, 67-69, and 71-73.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 66, 76, 78, 80 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP § 2144 and § 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

McKinney does not teach the use of the structural coordinate data of Appendix 3 as recited in the instant claims. However, this particular data required by the instant claims is considered to be nonfunctional descriptive material. In *Gulack* and *Ngai*, the respective Courts held that nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. According to *Gulack,* the key

factor in analyzing the obviousness of the claims over the prior art is the determination that the machine-readable data comprising the structural coordinates of Appendix 3 is a known machine-readable medium and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. According to MPEP 2106.01, "'functional descriptive material' consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of 'data structure' is 'a physical or logical relationship among data elements, designed to support specific data manipulation functions'" and that "'Nonfunctional descriptive material" includes but is not limited to music, literary works, and a compilation or mere arrangement of data.'" In this case, the data of Appendix 3 is an arrangement of data that represents a 3-D molecular structure. The data of Appendix 3 is not a data structure or a computer program that imparts functionality when employed as a computer component. The Appendix 3 structural coordinates are regarded as non-functional descriptive material and the claimed method is the same as the method of McKinney. The data of Appendix 3, which are processed using a series of processing steps using a known algorithm, do not appear to impose a change in the processing steps or functioning of the computer and there is no evidence of record that the data of Appendix 3 imposes a change in the function of the computer. Put another way, the function of the computer is the same whether the computer comprises the data of Appendix 3 or not. Thus, all claim limitations concerning the structure coordinate data

of Appendix 3 are given no patentable weight as the data is considered to be non-functional descriptive material.

McKinney discloses the teachings as described above.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the method as disclosed by McKinney using any set of structural coordinates as defined in the claims with a reasonable expectation of success in view of the teachings of McKinney. One would have been motivated to do this because McKinney discloses "The multifunctional ligand-receptor model concept should also be considered in the study of structure-activity relationships --- for other hormonal systems such as the steroid hormones" (see page 333, right column, bottom), wherein McKinney notes that "TBPA and at least one thyroid hormone nuclear receptor have a considerable number of their properties in common or have aspects of similarity" (see page 330, left column, lines 14-16) and further notes that "Studies of TBPA and the thyroid hormone nuclear receptor suggested that possibility of a closer relationship between the two proteins than would have been anticipated, which suggests that the studies on TBPA may have a direct bearing on the properties of the nuclear receptor" (see p. 327, right column bottom).

23. Claims 75, 77, 79, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336).

McKinney teach as described above.

McKinney does not teach a screening compounds in a biological assay for TR isoform activity.

McKinney states a molecules "T3 agonist/antagonist" and "T4 agonist/antagonist" (see middle of left column, p. 332) and suggest "the importance of T3 relative to T4 in thyroid hormone action is largely attributed to its greater hormonal potency when studied *in vivo* and its greater binding affinity to the nuclear thyroid hormone receptor *in vitro* studies" (see bottom of right column, p. 332 to top left column, p. 333). It would have been obvious to one of ordinary skill in the art at the time the invention was made to screen a test compound of McKinney to a TR LBD isoform with a reasonable expectation of success because a test compound is identified to have favorable interaction as indicated in receptor model shown in Figure 5, p. 331. The motivation to do so is provided by McKinney's disclosure of thyroid hormones "has recently been suggested -- - be part of the hormone responsive transcription factor super-family" (see page 330, middle of right column) and further that one would have validated the modeling results of McKinney with a biological assay. Thus, the claimed invention taken as a whole is *prima facie* obvious over the combined teachings of the prior art.

Additional References

17. The following are cited to complete the record but is not prior art:

a) Wagner *et al.* (1995, December 14) A structural role for hormone in the thyroid hormone receptor, Nature, vol. 378, p. 690-697. *This publication contains identical protein crystal as the instant application.*

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
October 24, 2006

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER

BRUCE KISLIUK, DIRECTOR
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10827121	Applicant(s) Baxter et al.	
	Examiner Alexander Kim	Art Unit 1656	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See next page.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
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7. Other: (cont.)

The structural coordinates in Appendix 3-8 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID No. must be inserted into the brief description of the drawings or into the Figure directly.

The SEQ. ID NOs are missing for each polypeptide in Figure 3.